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Systemic Lupus Erythematosus

Review

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Systemic lupus erythematosus (SLE) is considered to be the prototypic systemic autoimmune disease. In contrast to autoimmune diseases such as multiple sclerosis and type 1 diabetes mellitus, SLE has the potential to involve multiple organ systems directly, and its clinical manifestations are extremely diverse and variable (reviewed by Kotzin and O'Dell, 1995). For example, some patients may demonstrate predominantly skin rash and joint pain, show spontaneous remissions, and require little medication. The other end of the spectrum includes patients who demonstrate severe and progressive kidney involvement (glomerulonephritis) that requires therapy with high doses of steroids and cytotoxic drugs such as cyclophosphamide. Criteria for the classification of SLE have been established to facilitate the uniform reporting of SLE cases in studies. However, a multitude of different phenotypes are encompassed within this classification, and it remains unclear whether SLE represents a single pathologic entity with variable expression or a group of related conditions. This heterogeneity has greatly confounded studies of genetic associations and pathogenic mechanisms.

Although SLE can occur at nearly any age, women of childbearing age are primarily affected. The female to male ratio is greatest (>8:1) for patients presenting between ages 15 to 50 years, whereas the ratio is closer to 2:1 for disease that develops during childhood or after menopause. Incidence rates for patients and studies in certain animal models support a role for estrogens enhancing and androgens protecting against disease development. In the United States, the chance of a caucasian female developing SLE in her lifetime is approximately 1 in 700, and the incidence may be two to four times greater for blacks and hispanics. The overall prevalence of SLE ($\sim$1 in 2000) is about the same as multiple sclerosis and about 5- to 10-fold less than type 1 diabetes mellitus and rheumatoid arthritis.

The common denominator among SLE patients is immunoglobulin G (IgG) autoantibody production, and the hallmark of this disease is elevated serum levels of antibodies to nuclear constituents (i.e., anti-nuclear antibodies). In contrast to the other autoimmune diseases discussed in this review series, T cells do not appear to play a direct role in tissue damage in SLE, although, as discussed below, T cells are clearly involved in the development of autoantibody production. Figure 1 presents a conceptual framework for the pathogenesis of SLE, and the major events in this model provide the basis for the discussion below.

Studies using several animal models have contributed greatly to the elucidation of SLE pathogenesis (reviewed by Theofilopoulos and Dixon, 1985; Cohen and Eisenberg, 1991). Examples include the F1 hybrid of New Zealand black (NZB) and New Zealand white (NZW) mice, MRL mice homozygous for the lymphoproliferation (*lpr*) gene (MRL-*lpr*/*lpr*), and BXSB mice, which carry the disease-accelerating *Yaa* gene on the Y chromosome. These different strains are primarily models of lupus-like glomerulonephritis associated with the production of IgG antibodies to DNA.

Autoantibody Production and Disease Manifestations

Among the myriad of autoantibodies produced in SLE, principal targets include certain protein–nucleic acid complexes, notably chromatin, the U1 and Sm small nuclear ribonucleoprotein (snRNP) particles, and the Ro/SSA and La/SSB RNP complexes (reviewed by Tan, 1989; Kotzin and O'Dell, 1995). The multivalent nature of these complexes and their ability to cross-link B cell receptors as well as their concentration on apoptotic cells have been proposed as explanations for their preferential immunogenicity (Casciola-Rosen et al., 1994). Autoantibodies to phospholipids (complexed to β2 glycoprotein 1) are also relatively frequent and associated with thrombotic complications, a major clinical problem in some patients. A separate group of autoantibodies in SLE are directed to cell surface molecules. These latter specificities are easiest to understand in terms of their immunopathology, causing problems such as hemolytic anemia and platelet destruction (thrombocytopenia). The mechanism by which most autoantibodies in lupus may cause disease remains unclear. There is little evidence that anti-nuclear antibodies can readily penetrate cellular membranes and cause disease by binding to their intracellular targets. However, these autoantibodies may form immune complexes as described below for lupus nephritis, and a similar mechanism may be responsible for other disease manifestations such as arthritis, serositis, and vasculitis.

IgG autoantibodies to double-stranded DNA appear to play a prominent role in the immune complex glomerulonephritis of SLE (reviewed by Kotzin and O'Dell, 1995). Interestingly, anti-DNA antibodies do not appear to mediate renal damage through the deposition of circulating immune complexes, and two alternative theories have been proposed to explain their pathogenic mechanism. In the first, DNA initially binds to the glomerulus and is then recognized by anti-DNA antibodies, leading to in situ complex formation (Bernstein et al., 1995). In an alternative model, the subset of pathogenic anti-DNA antibodies is able to cross-react with glomerular structures that are not DNA in origin. Although most studies have focused only on anti-DNA antibodies in the cause of lupus nephritis, considerable evidence indicates that autoantibodies to non-DNA antigens are also important. For example, in the (NZB $\times$ NZW)F1 model,

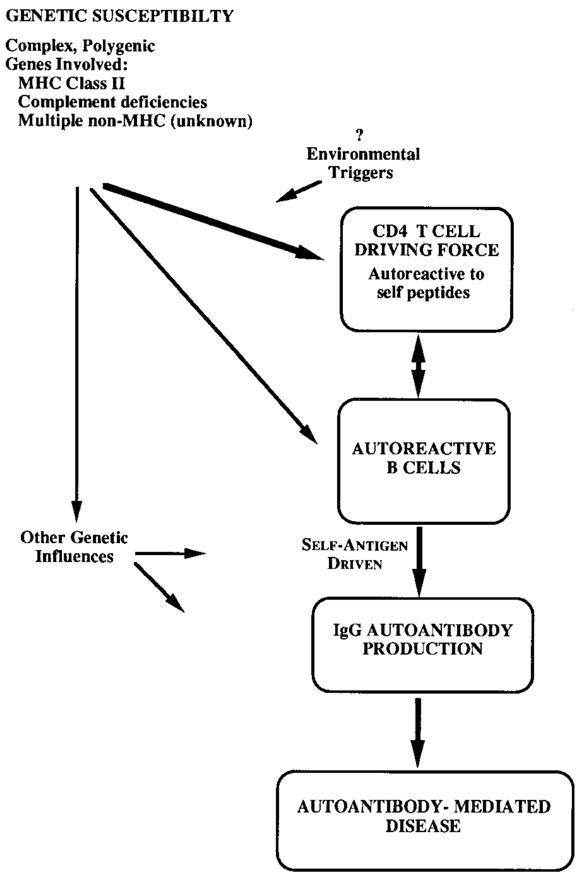

Figure 1. Hypothetical Scheme for Immunopathogenic Events in the Development of SLE

genetic studies have suggested a major pathogenic role for autoantibodies to the endogenous retroviral glycoprotein (gp70) and gp70–anti-gp70 immune complexes (Izui et al., 1981).

B Cell Tolerance and Activation in Lupus

Evidence strongly supports the conclusions that pathogenic IgG autoantibody production in SLE is selective for only certain self-antigens and that autoreactive B cells are driven by self-antigens. In SLE and lupus mice, studies have repeatedly shown that a subset of anti-DNA antibody–producing B cells are clonally expanded and that their immunoglobulin genes are modified by somatic mutation (reviewed by Radic et al., 1993). This process mimics a normal T cell–dependent response to foreign antigen, involving common mechanisms of somatic mutation, affinity maturation, and IgM to IgG class switching. Studies have shown that anti-DNA antibodies in lupus preferentially utilize certain V_H and V_L genes. Analysis of their complementarity-determining regions (CDRs), especially CDR3, have shown an increased number of arginine residues that enhance the binding of antibody to DNA and suggest selection by DNA itself (Radic et al., 1993). That self-antigen is involved in anti-nuclear antibody production in lupus is further supported by studies showing that multiple epitopes on the same autoantigen particle (e.g., chromatin or Sm/U1RNP) have been targeted by the autoantibody response.

Experiments with mice expressing transgenes encoding self-reactive antibodies have demonstrated that B cell development involves a process of tolerance that deletes or functionally inactivates autoreactive cells, including some specificities characteristic of SLE (reviewed by Goodnow et al., 1995; Chen et al., 1995). However, it is important to note that provision of a powerful CD4 T cell driving force is sufficient for lupus-like IgG autoantibody production and disease to develop in normal animals. This is observed, for example, in models of chronic graft-versus-host disease in which the transferred T cells are alloreactive, and these studies indicate that potentially pathologic B cells are part of the peripheral repertoire or rapidly develop during this T cell–driven process. Thus, defects in central B cell tolerance do not appear to be necessary to allow for lupus-like autoantibody production. Furthermore, the ability of normal animals to generate autoantibody responses that spread to multiple determinants on a particular nuclear complex after immunization with one peptide or component of this complex also supports this conclusion (Bockenstedt et al., 1995; Topfer et al., 1995; James et al., 1995).

CD4 T Cell Dependence of Autoantibody Production

The association of SLE with particular class II major histocompatibility complex (MHC) alleles and the affinity maturation of IgG autoantibody production in this disease strongly suggest that CD4 T cells are important in the pathogenesis of disease. Furthermore, in all of the major murine models, treatment with anti-CD4 antibodies can ameliorate IgG autoantibody production and disease. Additional studies indicate that blocking T cell activation or T cell–B cell interactions will also prevent autoantibody production and disease (Finck et al., 1994; Mohan et al., 1995). The specificities of the autoreactive T cells, however, have not been well characterized, and the nature of T cell help in SLE may indeed differ from conventional responses. In the anti-DNA response, it seems unlikely that T cells directed to DNA determinants are operative. Studies in murine lupus have shown that a non-DNA nucleosomal antigen stimulates some autoreactive T cells that drive anti-DNA antibody–producing B cells (Mohan et al., 1993). Thus, a DNA-specific B cell could bind and internalize nucleosomes, with subsequent class II MHC presentation of histone or other chromosomal peptides to T cells. In other studies, immunoglobulin peptides derived from an IgG anti-DNA autoantibody were shown to stimulate T cells from (NZB $\times$ NZW)F1 mice and enhance IgG anti-DNA antibody production (Singh et al., 1995).

In studies relevant to organ-specific autoimmune diseases such as multiple sclerosis and type 1 diabetes mellitus, the evidence indicates that autoimmune and potentially disease-causing T cells are present in the normal peripheral T cell repertoire. Thus, these T cells were not deleted during normal development in the thymus, and their inactivity appears to be maintained by protective mechanisms of peripheral tolerance—functional inactivation, immunoregulation, and immunological ignorance. The same scenario may exist for lupus-relevant T cells despite the ubiquitous nature of the target autoantigens. Studies in lupus mice, for example, have suggested that high affinity responses to self-antigens are tolerized normally in the thymus (Herron et al., 1993). Other work has indicated that dominant determinants of a self-antigen that are processed and presented efficiently in the thymus will be effective tolerogens, but T cells directed to cryptic self-determinants may escape tolerance induction and be part of the normal peripheral T cell repertoire (reviewed by Sercarz et al., 1993). Therefore, abnormal presentation of such cryptic determinants in the periphery or a defect in peripheral T cell tolerance in SLE could allow activation of autoimmune T cells. Immunization of normal mice with cryptic peptides of a self-nuclear antigen has been shown to result in lupus-like autoantibody production (Bockenstedt et al., 1995).

Patterns of cytokine production by T cells appear to be critically important in diseases such as multiple sclerosis and type 1 diabetes. These diseases appear to be dependent on Th1-type responses, and deviation from this pattern may lead to protection from disease expression. In SLE, Th2-type responses may be important in disease development, as demonstrated in the chronic graft-versus-host model of disease. However, in spontaneous murine models, the IgG isotypes most important for pathogenicity (IgG2a, IgG2b, and IgG3) suggest the additional influence of Th1-type cytokines and the importance of interferon-γ. Although there is a wealth of data regarding defects in cytokine production and immunoregulatory T cells in SLE, it is not clear at this time whether any are primary to the pathologic process.

Environmental Triggers and Influences

Environmental influences on the expression of disease manifestations are clearly seen in SLE. These include the exacerbation of skin rash (or even systemic symptoms) after sun exposure, exacerbations of disease after viral or bacterial infections, and changes in disease activity after administration of exogenous hormones. It is also clear that chronic treatment of patients with certain drugs (such as procainamide or hydralazine) can induce the production of anti-nuclear antibodies and a lupus-like disease (reviewed by Kotzin and O'Dell, 1995) and that intraperitoneal injection with pristane (2,6,10,14-tetramethylpentadecane) can induce a lupus-like disease in normal mice (Satoh et al., 1995). Despite this information, there is no clear evidence that an environmental trigger is involved in the initiation of human SLE. The fact that approximately 75% of monozygotic twins are discordant for disease expression has also been used as evidence to support the existence of an environmental stimulus. However, mouse strains can also be created such that 25% reproducibly develop disease or produce particular autoantibodies, and careful examination of positive mice has excluded environmental effects as the major factor in variable expression (Eisenberg et al., 1987; Drake et al., 1995). In these mice, the probability of disease appears to be totally genetically determined, and unknown stochastic (random) events determine which will develop disease. Overall, the importance of environmental triggers in human SLE remains unclear.

Genetic Contributions

Many aspects of the genetic basis of lupus are reviewed in a separate paper in this series. Even when one animal model and one phenotype is being considered, the genetic basis of lupus-like disease is remarkably complex, involving contributions from multiple genes in addition to class II MHC (Drake et al., 1995; Morel et al., 1994; Kono et al., 1994). Furthermore, it seems likely that different genetic contributions are operative in different animal models (and therefore in different patients), even when the same phenotype is being followed. Some traits appear to be determined in a threshold manner (Morel et al., 1994; Drake et al., 1995). Thus, the particular combination of genes may be less important than just the accumulation of an adequate number of predisposing genes. An additional complexity relates to the fact that contributions are unlikely to represent genetic mutations rather than polymorphic alleles with subtle functional differences. Related to this issue, in some analyses of genes from lupus-prone strains, genes from the normal strain can be shown to have enhancing effects on disease expression (Drake et al., 1995).

In addition to class II MHC genes, there is evidence that genetically determined complement deficiencies also contribute to disease susceptibility in a subset of SLE patients. The mechanism for this influence is unknown. Some investigators have postulated defects in the clearance of infectious particles or immune complexes, leading to enhanced autoantibody production. Alternatively, complement gene defects may exemplify genetic influences that operate distal to autoantibody production, and similar genetic contributions appear to be present in murine lupus nephritis. For example, these genetic contributions may allow enhanced deposition or formation of immune complexes in the kidney or possibly affect the inflammatory response or end-organ response to complexes.

A possible step forward in understanding genetic contributions in lupus relates to the identification of *lpr* and *gld* as mutations in Fas and Fas ligands, respectively, which are involved in programmed cell death (apoptosis) (reviewed by Cohen and Eisenberg, 1991; van Houten and Budd, 1994). Homozygosity for these mutations results in the acceleration of lupus-like autoimmunity as well as a massive accumulation of $CD4^-$ $CD8^-$ (double negative) T cells. Full expression of lupus-like disease in MRL-*lpr*/*lpr* mice is dependent on contributions from other non-MHC genes. Although the mechanism by which mutations in Fas lead to accelerated autoimmunity is unknown, the strongest hypothesis is that self-reactive T and B cells arise when they fail to undergo apoptosis normally. Studies have shown that both T cells and B cells must carry the *lpr* mutation for maximal autoantibody production to occur. Fas may not be important in intrathymic tolerance during T cell development, and studies support the contention that peripheral T cell tolerance mechanisms are primarily affected by the *lpr* mutation (Herron et al., 1993; Singer and Abbas, 1994). Studies suggest that central B cell tolerance also may be relatively independent of Fas, and surface expression of Fas on B cells may be most important in preventing inappropriate CD4 T cell–dependent expansion of autoreactive B cells in the periphery (Goodnow et al., 1995; Rathmell and Goodnow, 1994; Rathmell et al., 1995; Rothstein et al., 1995). *Fas* mutations have been identified in a few children with lymphoproliferative syndromes and evidence of autoimmunity. However, it is important to emphasize that there is really no counterpart to the *lpr* or *gld* phenotype in human SLE, and recent studies have not found defects of these genes in SLE patients. Still, there is a belief that other genes involved in apoptosis or related cell signaling pathways may be involved in the emergence of autoreactive lymphocytes and genetic susceptibility in the human disease.

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